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EXAMINER
WHITEMAN, BRIAN A

ART UNIT	PAPER NUMBER
1633	6

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/838,718	STEIDLER ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *5 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-12 and 14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Priority

Application claims priority to PCT/EP99/07800 filed on 10/6/99 is acknowledged. However, this application is a CON of PCT/EP99/07800, which claims priority to an EPO document 98203529.7 filed on 10/20/1998 and the document is missing so applicants cannot enjoy benefit of foreign priority under 35 USC 119(a-d) to the EPO document.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-20, drawn to a method of treating inflammatory bowel disease in a subject, said method comprising: administering a medicament comprising an amount of a cytokine-producing Gram positive bacterial strain to a subject; a genetically engineered Gram-positive bacterial strain, said genetically engineered Gram-positive bacterial strain engineered to express a cytokine, classifiable in class 424, subclass 93.2.

II. Claims 1-20, drawn to a method of treating inflammatory bowel disease in a subject, said method comprising: administering a medicament comprising an amount of a cytokine-antagonist Gram positive bacterial strain to a subject, a genetically engineered Gram-positive bacterial strain, said genetically engineered Gram-positive bacterial strain engineered to express a cytokine antagonist, classifiable in class 424, subclass 93.2.

Claims 1 and 19 link inventions I and II. The restriction requirement between the linked inventions is subject to the non-allowance of the linking claim(s), claims 1 or 19. Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be

withdrawn and any claim(s) depending from or otherwise including all the limitations of the allowable linking claim(s) will be entitled to examination in the instant application. Applicant(s) are advised that if any such claim(s) depending from or including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or non-statutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

The inventions are distinct, each from the other because:

Although there are no provisions under the section for "Relationship of Inventions" in MPEP 806.05 for inventive groups that are directed to different methods, restriction is deemed to be proper because each of the methods of inventions I and II, constitutes patentably distinct inventions for the following reasons: Each of the inventions is directed to different goals and comprises materially distinct steps, wherein each of the compositions in each invention is structurally distinct and/or generates distinct mechanisms and functional effects as indicated above. The scope of each of the cited inventions encompasses an employed method, which generates distinct function(s) and effect(s), and furthermore does not necessarily overlap with that of another invention. Furthermore, invention I is a method of treating inflammatory bowel disease in a subject, said method comprising: administering a medicament comprising an amount of a cytokine-producing Gram positive bacterial strain to a subject; invention II is directed to a method of treating inflammatory bowel disease in a subject, said method comprising:

administering a medicament comprising an amount of a cytokine-antagonist Gram positive bacterial strain to a subject. Inventions I and II comprise materially distinct steps, and/or generate different functions and effects, and thus, are not required for use with one another. Therefore the invention of group I is distinct from group II.

If applicants' elect Group I, claim 1 is generic to a plurality of disclosed patentably distinct species comprising Gram-positive bacterial strain selected from a Lactococcus species (claim 3), Bacillus subtilis (claim 5), Streptococcus gordonii (claim 5), Staphylococcus xylosus (claim 5), and a Lactobacillus spec (claim 5). Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

If applicants' elect Group I, claim 1 is generic to a plurality of disclosed patentably distinct species in claim 6 comprising bowel disease consisting of chronic colitis, Crohn's disease, and ulcerative colitis. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

If applicants' elect Group I, claim 1 is generic to a plurality of disclosed patentably distinct species in claim 8 and claim 16 comprising another therapeutic agent selected from the group consisting of corticosteroids, suplhasalzine and derivatives of sulphasalzine, immunosuppressive drugs, cyclosporin A, meracaptopurine, azathioprine, and another cytokine. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

If applicants' elect Group I, claim 2 is generic to a plurality of disclosed patentably distinct species comprising IL-10, a soluble TNF receptor, or another TNF antagonist, an IL-12 antagonist, an IL-1 antagonist, a virus-coded cytokine analogue, and EBV BRCF1. Applicant is

required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

If applicants' elect Group I, claim 19 is generic to a plurality of disclosed patentably distinct species comprising Gram-positive bacterial strain selected from a Bacillus subtilis, Streptococcus gordonii, Staphylococcus xylosus, and a Lactobacillus spec. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

If applicants' elect Group I, claim 19 is generic to a plurality of disclosed patentably distinct species comprising cytokine selected from the group consisting of IL-10, a soluble TNF receptor or another TNF antagonist, and IL-12 antagonist, an Interferon-γ antagonist, an IL-1 antagonist, a virus-coded cytokine analogue, and EBV BRCF1. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

If applicants' elect Group II, claim 1 is generic to a plurality of disclosed patentably distinct species comprising Gram-positive bacterial strain selected from a Lactococcus species (claim 3), Bacillus subtilis (claim 5), Streptococcus gordonii (claim 5), Staphylococcus xylosus (claim 5), and a Lactobacillus spec (claim 5). Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

If applicants' elect Group II, claim 1 is generic to a plurality of disclosed patentably distinct species in claim 6 comprising bowel disease consisting of chronic colitis, Crohn's disease, and ulcerative colitis. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

If applicants' elect Group II, claim 1 is generic to a plurality of disclosed patentably distinct species in claim 8 and claim 16 comprising another therapeutic agent selected from the group consisting of corticosteroids, suplhasalzine and derivatives of sulphasalzine, immunosuppressive drugs, cyclosporin A, meracaptopurine, azathioprine, and another cytokine. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

If applicants' elect Group II, claim 2 is generic to a plurality of disclosed patentably distinct species comprising IL-10, a soluble TNF receptor, or another TNF antagonist, an IL-12 antagonist, an IL-1 antagonist, a virus-coded cytokine analogue, and EBV BRCF1. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

If applicants' elect Group II, claim 19 is generic to a plurality of disclosed patentably distinct species comprising Gram-positive bacterial strain selected from a Bacillus subtilis, Streptococcus gordonii, Staphylococcus xylosus, and a Lactobacillus spec. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

If applicants' elect Group II, claim 19 is generic to a plurality of disclosed patentably distinct species comprising cytokine selected from the group consisting of IL-10, a soluble TNF receptor or another TNF antagonist, and IL-12 antagonist, an Interferon-γ antagonist, an IL-1 antagonist, a virus-coded cytokine analogue, and EBV BRCF1. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

It would be unduly burdensome for the examiner to search and consider patentability of all of the presently pending claims, a restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 § 1.17(h).

During a telephone conversation with Mr. Allen Turner on December 12, 2001, a provisional election was made without traverse to prosecute the invention of Group I, claims 1-20 and the species election encompassing Lactococcocus sp (claim 3), Crohn's disease (claim 6), immunosuppressive drugs (claims 8 and 16), IL-10 (claim 2), Lactobacillus spec (claim 19), and

IL-10 (claim 19). Affirmation of this election must be made by applicant in replying to this office action.

Claims 5, 13, and the non-elected species are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Election was made **without** traverse.

Claim Objections

Claims 9 and 17 are objected to because of the following informalities: Claims 9 and 17 are objected to for reciting grammatically improper phase, "co-administration of the at least." Amending the claim to recite "co-administration of at least," would obviate this objection. Appropriate correction is required.

Elected claims 1-4, 6-12, and 14-20, are pending examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-12 and 14-20 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A method of treating colitis in a mammal, comprising administering a medicament comprising an amount of a genetically modified Lactococcus lactis expressing Il-10 to a mammal with colitis by injected said recombinant Lactococcus lactis into the peritoneum of said mammal, wherein ~~the treatment~~ RWI/1/10 said administration results in an increase in colon length and reduced epithelial damage and infiltration of lymphocytes in said mammal with colitis, 2) The method of 1, wherein the medicament is administered in combination with at

least one additional anti-colitis drug, and does not reasonably provide enablement for other claimed embodiments embraced by the breadth of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants are reminded that intended use such for claim 20 have patentable weight for enablement, while intended use have little or no relevant weight for art purposes. Claim 20 is examined here for the phrase: "pharmaceutical."

The claims of the instant application are directed to a method of treating a mammal by methods of ex vivo gene therapy by administering a composition to the mammal consisting of, a bacterium that expresses a recombinant gene, encoding a therapeutic protein, wherein the bacterium is a cytokine producing gram-positive bacteria.

Furthermore, and with respect to claims directed to any vector useful for gene therapy and directed to any treatment of a mammal; the state of the art in 1998, exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Thus, gene therapy was considered unpredictable at the time the application was filed.

Specifically, the specification contemplates a cytokine-producing Gram-positive bacterial strain can be used for the preparation of a medicament to treat inflammatory bowel disease. More specifically, the specification specifically teaches a recombinant Lactococcus lactis (L. lactis) comprising a gene encoding an IL-10 protein. The recombinant bacteria are then injected

in to the peritoneum of healthy mice or mice with induced colitis. The pathology of chronic colitis is characterized by a decrease in colon length and epithelial damage and infiltration of lymphocytes. Example 2, mice are euthanized and a histological score of the colon demonstrates an increase in colon length of the mice with induced colitis after the treatment with the recombinant IL producing L. lactis compared to mice with induced colitis and untreated and control mice. The specification also demonstrates the prevention of colitis in IL10-/-mice by intra-gastric inoculation with IL-10 producing L. lactis (Example 5, pages 17-18 and Figure 10).

The specification provides sufficient guidance for one skilled in the art to treat colitis using an engineered Il-10 producing Lactococcus lactis in a mammal, wherein the treatment consist of observing an increase in colon length and reduced epithelial damage and infiltration of lymphocytes compared to an untreated mammal with colitis. In addition with respect to the claimed invention, the claims broadly encompass the use of any species of genetically modified cytokine producing Gram-positive bacterial strain. The specification and the state of the art provide sufficient guidance for one skilled in the art to genetically modify either Bacillus subtilis or Lactococcus lactis; however, the disclosure does not provide sufficient guidance on manipulating any other species of bacteria including Bacillus subtilis to achieve successful expression of a functioning protein (e.g. Il-10). It is well known in the art of recombinant DNA technology, that there are no methods available to successfully transform all species of cytokine-producing Gram positive bacteria and that several types of Gram positive bacteria do not possess the qualities necessary to achieve such transformation. Therefore, it would require one skilled in the art an undue amount of experimentation to develop techniques to transform a representative number of bacteria species other than Lactococcus or Bacillus.

The claimed inventions invention encompasses a genus of gram positive bacteria that the specification and prior art only provide sufficient guidance for one skilled in the art to make and/or use the Lactococcus lactis in a method of treating colitis in a mammal comprising genetically modifying the Lactococcus to produce IL-10. However, in view of the breadth of the claims, the disclosure and the state of the art do not provide sufficient guidance for one skilled in the art to make and/or use a representative number of Gram-positive bacteria (e.g. Staphylococcus aureus, Enterococcus spp, and Streptococcus pneumoniae) in a method of treating colitis because the use of Gram-positive bacteria other than L. lactis in a method of ex vivo gene therapy would require knowledge about control expression in vivo of a representative number of Gram-positive bacteria and knowledge that the bacteria would not harm the mammal before a treatment of colitis could be observed. Therefore, it would require an undue amount of experimentation to reasonably extrapolate to any Gram-positive bacteria other than L. lactis.

Furthermore, with respect to claims 19 and 20, which encompass a genetically engineered Lactobacillus species expressing IL-10 or a pharmaceutical composition comprising a genetically engineered Lactobacillus species expressing IL-10, in view of the specification, the only intended use of this recombinant bacterium is in a method of treating an inflammatory bowel disease. The specification and the state of the art provide sufficient guidance for one skilled in the art to make a recombinant bacterium (see Pouwels et al. *Antonie van Leeuwenhoek*, Vol. 64, pp. 85-107, 1993), however, the disclosure does not provide sufficient guidance for one skilled in the art to use any recombinant bacterium other than L. lactis in a method of ex vivo gene therapy for treating an inflammatory bowel disease because it is not apparent that the IL10 protein would be functionally expressed by bacteria to provide a therapeutic effect. For example, proteins

produced in prokaryotes do not always retain eukaryotic function because prokaryotes cannot post-translationally modify proteins. Furthermore, it is unclear how the examples in the disclosure reasonably correlate to using any other cytokine producing Gram-positive bacteria other than the Lactobacillus species expressing IL-10 in view of the concerns listed above.

In addition, in view of the breadth of the claims, the claimed invention encompasses that any cytokine can be used in a method of treating colitis. The state of the art and the specification provide sufficient guidance for one skilled in the art to make and/or use a nucleic acid encoding the Il-10 protein in a method of treating colitis, however, the specification lacks sufficient guidance for one skilled in the art to make and/or use any other cytokine in a method treating colitis, wherein the treatment consist of observing an increase in colon length and reduced epithelial damage and infiltration of lymphocytes compared to an untreated mammal with colitis. The state of the art provides numerous cytokines (See Kuby, Immunology, pages 304-306, 1994) and their properties, however, the specification lacks sufficient guidance for one skilled in the art to use any cytokine other than IL-10 in an ex vivo method of gene therapy comprising obtaining a genetically modified L. lactis comprising a nucleic acid encoding a cytokine. Thus, it would take one skilled in the art an undue amount of experimentation to reasonably correlate the results observed with using Il-10 to any other cytokine.

Furthermore in view of doubts expressed in Anderson and Verma encompassing gene therapy and in view of the breadth of the term treating (treating/preventing), the state of art for preventing exemplified by McCluskie et al. (*Molecular Medicine*, 5, pp. 287-300, 1999) teach that "the realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in non-human primates", that "IM injection of plasmid

DNA vaccines, while highly immunogenic in mice...was found only to be relatively so in chimpanzees..., and especially not all in Aotus monkeys'" and that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but note necessarily vice-versa" (page 296, column 2, second and third paragraphs). In addition, McCluskie et al. teach that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predicative they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological reponses to the antigen" (page 297, column 1).

Thus, it is not apparent as how one skilled in the art reasonably extrapolates, without undue experimentation, from the scope of mammal to the full scope of the claimed invention that would generate a treatment (encompasses partial/complete protection) and/or prevention (total protection) in any subject against any inflammatory bowel disease. Even if a protective response has been shown in mice using the exemplified mice, it is not apparent as to how the mouse model is reasonably extrapolated to the full scope of the claimed invention, encompassing any subject particularly given that there is no vaccine generation evidence showing that the mice model is a general phenomenon, and given the doubts expressed in the art of record.

In addition with respect to claims encompassing a method of treating any subject for treatment (encompasses partial/complete protection) or prevention (total protection) wherein any administration route is contemplated. The application only provides sufficient guidance and/or factual evidence demonstrating the prevention of colitis in IL10-/-mice by intra-gastric inoculation with IL-10 producing L. lactis (Example 5, pages 17-18 and Figure 10). Furthermore, the specification states, "The cause of inflammatory bowel diseases is unknown"

(page 4). Thus, since the cause of inflammatory bowel disease is unknown, it would require one skilled in the art an undue amount of experimentation to identify which mammal is susceptible to an inflammatory bowel disease.

With respect to therapeutic methods (vaccination or ex vivo gene therapy) encompassing routes of administration, the state of the art exemplified by Verma and in further view of McCluskie, who teaches that the route of delivery of the DNA vaccine can have an impact on the efficiency of transfection as well as the types and location of cells transfected, and thus potentially on the nature of the immune response (pg. 295). In addition, McCluskie teaches that many different routes have been shown to be effective for DNA delivery in mice; however, few studies have compared responses obtained with different routes using the same antigen-expressing DNA, dose, and immunization schedule. There have been even fewer studies to compare routes of administration in non-human primates (pg. 295). Furthermore, it is unclear for the disclosure that recombinant bacteria administered through any route other the peritoneum route would produce a therapeutic effect. For example, it is unclear how to avoid digestion of the bacterium, and the proteins they produce, when administered orally, or if bacteria delivered to the bronchia will produce proteins that will be absorbed and translocated to the appropriate tissue to achieve a therapeutic effect. Therefore an undue amount of experimentation would be required for one skilled in the art to determine routes of administration other than the peritoneum route to treat colitis encompassed by the claims.

Furthermore, with respect to claims 1-4, 7-12, and 14-20, which encompass treating a inflammatory bowel disease, the specification and the state of the art only provide sufficient guidance for how to treat colitis, which is a well characterized pathology of any inflammatory

bowel disease (IBD), e.g. Crohn's Disease, and the etiology remains poorly understood and several genetic and environmental factors have been implicated in the pathogenesis of IBD (Papadakis et al. Annu. Rev. Med., Vol. 51, pp.289-298, 2000). Furthermore, Crohn's Disease is an eponym that describes the convergence of many clinical signs and symptoms (Targan et al. Nature Medicine, Vol. 1, pp 1241, 1995). Thus, since only the clinical sign known as colitis has been well characterized and the etiology of treating any IBD is not fully understood, and the specification only provide sufficient guidance for one skilled in the art to make and use a genetically modified L. lactis expressing Il-10 for to treat colitis, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from treating the clinical sign colitis to treating any IBS, e.g. Crohn's Disease, encompassing numerous clinical signs or symptoms in a mammal.

In addition, it is not apparent as how one skilled in the art reasonably extrapolates, without undue experimentation, from the scope of mammals to the full scope of the claimed invention that would generate a treatment of colitis in a subjects (*e.g.* birds, fish, mammals, etc.). Even if a therapeutic response using an ex vivo method of gene therapy for colitis in an experimental murine model using peritoneum injection has been shown in the specification, it is not apparent as to how it is reasonably extrapolated to the full scope of the claimed invention, encompassing treating any type of inflammatory bowel disease in a subject.

At best, the application and the state of the art only provide sufficient guidance for enabling claims directed to 1) A method of treating colitis in a mammal, comprising administering a medicament comprising an amount of a genetically modified Lactococcus lactis expressing Il-10 to a mammal with colitis by injected said recombinant Lactococcus lactis into

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the peritoneum of said mammal, wherein ~~the treatment~~ said administration results in an increase in colon length and reduced epithelial damage and infiltration of lymphocytes in said mammal with colitis, 2) The method of 1, wherein the medicament is administered in combination with at least one additional anti-colitis drug.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable 1 and 2, listed above. One would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the application's disclosure, the unpredictability of gene therapy (Anderson, *Nature*, Vol. 392, pp.25-30, 1998) and developing effective vaccines encompassing any subject for a protective effect and/or treatment. In addition, the presence of a working example as provided in the specification does not extrapolate to the full scope of the claimed invention, particularly given that there is no evidence that the mice model is a general phenomenon.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 20 is directed to a pharmaceutical composition. The intended use of a product, in the instant claims for pharmaceutical compositions, does not have patentable weight for prior art rejections. An intended use does not provide an alteration to the genetically modified

Lactobacillus gram-positive bacterium expressing IL-10 that distinguishes it from that taught in the art of record.

Claims 1, 2, 3, 4, 6, 10, 11, 12, 14, 18, 19, and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Tagliabue et al. (Applicants' IDS, Tagliabue, WO 96/11277) as evidenced by Herfarth et al (*Gut*, Vol. 39, abstract, 1996). Tagliabue teaches methods and compositions for delivery of therapeutic protein using a gram-positive bacterium, wherein the bacterium is the Lactococcus species, L. lactis or Bacillus subtilis (page 11). Furthermore, Tagliabue teaches that the genetically modified bacterium can comprise a gene encoding an IL-1ra or IL-10 protein (page 15). Tagliabue further teaches that IL-1ra or IL-10 expressing bacteria can be used to treat colitis (page 17, lines 24-26). Tagliabue also teaches that the recombinant bacterium is suspended in a pharmaceutical formulation (pages 18-19). In addition, Tagliabue teaches in vivo examples comprising IL-1ra expressing Bacillus subtilis, which was injected intraperitoneally into mice (Example 4, pages 37-39). Since exogenous IL10 has been applied in the prior art to treat colitis as evident by Herfarth et al., Gut, Vol. 39, abstract, 1996, and the method and the composition taught by Tagliabue has all of the properties cited in the claims, then Tagliabue anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or non-obviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 7, 8, 9, 15, 16, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tagliabue (Applicants' IDS) taken with either Korelitz (The Gastroenterologist, Vol. 3, 1995, pp. 141-152) or Ferrante et al. (US Patent No. 6,262,119). Tagliabue teaches methods and compositions for delivery of therapeutic compounds to an animal by administration of a recombinant bacterium to the animal, the bacterium encoding the therapeutic protein (abstract). The microorganism is a gram-positive bacterium, wherein the bacterium is a Lactococcus species and L. lactis (pages 10-11). Tagliabue teaches that the composition can be used to treat colitis (page 17, lines 24-26). Furthermore, Tagliabue teaches that the genetically modified bacterium comprises a gene encoding an IL-10 protein. Tagliabue

further teaches that the recombinant bacterium is suspended in a pharmaceutical formulation (pages 18-19). However, Tagliabue does not teach a method of treating colitis in an animal, comprising administering a cytokine-producing Gram-positive bacteria further comprising administering in at least one additional agent, wherein the agent is selected from the group consisting of corticosteroids, sulphasalazine, immunosuppressive drugs, cyclosporin A, marcaptopurine, azathioprine, and another cytokine.

However, at the time the invention was made, drugs used to treat colitis include anti-inflammatory agents such as sulphasalazine (5-ASA) corticosteroids, cyclosporin A and azathiprine (column 3, lines 64-67). The immunosuppressive drugs anti-CD4 and anti-TNF monoclonal antibodies have been used to successfully treat ulcerative colitis (column 3 line 64-column 4 lines 1-4). Korelitz teaches that a patient with colitis was successfully treated with 6-mercaptopurine (6-MP), a metabolic product of azathioprine (page 141).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Tagliabue taken with either Korelitz or Ferrante, namely to produce a recombinant IL-10 producing Lactococcus lactis and use it in combination with additional therapy to treat colitis in a mammal. One of ordinary skill in the art would have been motivated to combine the recombinant Lactococcus lactis and any agent that was already well known in the art to treat colitis in a mammal for an additive effect.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. Tracey Johnson whose telephone number is (703) 305-2982. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, Debbie Clark can be reached at (703) 305-4051.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

Brian Whiteman
Patent Examiner, Group 1633
January 11, 2001